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Veröffentlicht
Mit internationalem Recherchenbericht.
Vor Ablauf der für Änderungen der Ansprüche zugelassenen Frist. Veröffentlichung wird wiederholt falls Änderungen eintreffen.

(54) Title: NOVEL SUBSTITUTED PYRAZOLE DERIVATIVES FOR THE TREATMENT OF CARDIOCIRCULATORY DISEASES

(54) Bezeichnung: NEUE SUBSTITUIERTE PYRAZOLDERIVATE ZUR BEHANDLUNG VON HERZKREISLAUFERKRANKUNGEN

(57) Abstract

The present invention relates to novel substituted pyrazole derivatives, a method for the production and the use thereof as a medicament, specially as a medicament to treat cardiocirculatory diseases.

(57) Zusammenfassung

Die vorliegende Erfindung betrifft neue substituierte Pyrazolderivate, Verfahren zu ihrer Herstellung und ihre Verwendung als Arzneimittel, insbesondere als Arzneimittel zur Behandlung von Herzkreislauferkrankungen.

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(19) **AUSTRALIAN PATENT OFFICE**

(11) Application No. **AU 199854823 B2**
(10) Patent No. **729642**

(54) Title
Novel substituted pyrazole derivatives for the treatment of cardiocirculatory diseases

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(57) Abstract

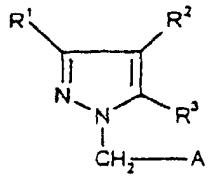
The present invention relates to novel substituted pyrazole derivatives, a method for the production and the use thereof as a medicament, specially as a medicament to treat cardiocirculatory diseases.

(57) Zusammenfassung

Die vorliegende Erfindung betrifft neue substituierte Pyrazolderivate, Verfahren zu ihrer Herstellung und ihre Verwendung als Arzneimittel, insbesondere als Arzneimittel zur Behandlung von Herzkreislauferkrankungen.

Patent claims

1. Substituted pyrazole derivatives of the general formula (I)



(I)

in which

R^1 represents a saturated or aromatic 5- or 6-membered heterocycle having up to 3 heteroatoms from the group consisting of S, N and/or O, which can be bonded via a nitrogen atom and which is optionally substituted up to 3 times identically or differently by amino, azido, formyl, mercaptyl, carboxyl, hydroxyl, straight-chain or branched acyl, alkoxy, alkylthio or alkoxycarbonyl each having up to 6 carbon atoms, nitro, cyano, halogen, phenyl or straight-chain or branched alkyl having up to 6 carbon atoms, which for its part can be substituted by hydroxyl, amino, azido, carboxyl, straight-chain or branched acyl, alkoxy, alkoxycarbonyl or acylamino each having up to 5 carbon atoms or by a radical of the formula $-OR^4$,

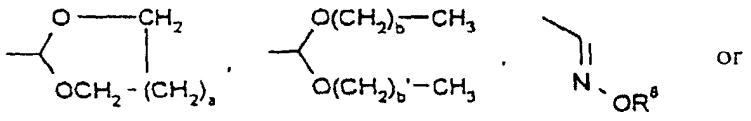
in which

R^4 denotes straight-chain or branched acyl having up to 5 carbon atoms or a group of the formula $-SiR^5R^6R^7$,

in which

R^5, R^6 and R^7 are identical or different and denote aryl having 6 to 10 carbon atoms or alkyl having up to 6 carbon atoms,

and/or is substituted by a radical of the formula



or

$-S(O)_c-NR^9R^{10}$,

in which

a, b and b' are identical or different and denote a number 0, 1, 2 or 3,

R^8 denotes hydrogen or straight-chain or branched alkyl having up to 4 carbon atoms,

c denotes a number 1 or 2 and

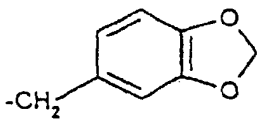
R^9 and R^{10} are identical or different and denote hydrogen or straight-chain or branched alkyl having up to 10 carbon atoms, which can optionally be substituted by cycloalkyl having 3 to 8 carbon atoms or by aryl having 6 to 10 carbon atoms, which for its part can be substituted by halogen, or

denote aryl having 6 to 10 carbon atoms, which is optionally substituted by halogen, or

denote cycloalkyl having 3 to 7 carbon atoms, or

R^9 and R^{10}, together with the nitrogen atom, form a 5- to 7-membered saturated heterocycle which can optionally contain a further oxygen atom or a radical $-NR^{11}$, in which

R^{11} denotes hydrogen, straight-chain or branched alkyl having up to 4 carbon atoms or a radical of the formula



or denotes benzyl or phenyl, where the ring systems are optionally substituted by halogen,

R^2 and R^3, including the double bond, form a 6-membered saturated or aromatic heterocycle having up to 3 heteroatoms from the group consisting of N, S and/or O, which is optionally substituted up to 3 times identically or differently by formyl, carboxyl, hydroxyl, mercaptyl, straight-chain or branched acyl, alkylthio or alkoxycarbonyl each having up to 6 carbon atoms, nitro, cyano, halogen or straight-chain or branched alkyl or alkoxy each having up to 6 carbon atoms, which for its part can be substituted by hydroxyl, amino, carboxyl, straight-chain or branched acyl, alkoxy or alkoxycarbonyl each having up to 5 carbon atoms,

and/or the heterocycle is optionally substituted by a group of the formula $-NR^{12}R^{13}$ or $-S(O)_c NR^{9'}R^{10'}$, in which

R^{12} and R^{13} are identical or different and denote hydrogen or straight-chain or branched alkyl having up to 6 carbon atoms, or

R^{12} denotes hydrogen and

R^{13} denotes formyl

c', $R^{9'}$ and $R^{10'}$ have the meaning of c, R^9 and R^{10} indicated above and are identical to or different from these

and/or the heterocycle is optionally substituted by phenyl which for its part can be substituted up to 2 times identically or differently by halogen or by straight-chain or branched alkyl or alkoxy each having up to 6 carbon atoms

and/or the heterocycle is optionally substituted by a group of the formula $-N=CH-NR^{14}R^{15}$, in which

R^{14} and R^{15} are identical or different and denote hydrogen, phenyl or straight-chain or branched alkyl having up to 6 carbon atoms,

A represents a 5- or 6-membered aromatic or saturated heterocycle having up to 3 heteroatoms from the group consisting of S, N and/or O or phenyl, each of which is optionally substituted up to 3 times identically or differently by amino, mercaptyl, hydroxyl, formyl, carboxyl, straight-chain or branched acyl, alkylthio, alkyloxyacyl, alkoxy or alkoxycarbonyl each having up to 6 carbon atoms, nitro, cyano, trifluoromethyl, azido, halogen, phenyl or straight-chain or branched alkyl having up to 6 carbon atoms, which for its part can be substituted by hydroxyl, carboxyl, straight-chain or branched acyl, alkoxy or alkoxycarbonyl each having up to 5 carbon atoms,

and/or is substituted by a group of the formula $-(CO)_d-NR^{16}R^{17}$,

in which

d denotes a number 0 or 1,

R^{16} and R^{17} are identical or different and

denote hydrogen, phenyl, benzyl or straight-chain or branched alkyl or acyl each having up to 5 carbon atoms,

and their isomeric forms and salts.

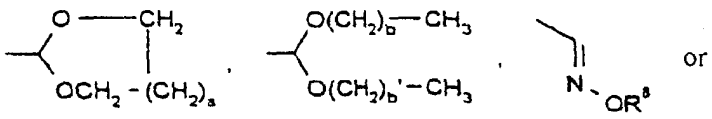
2. Compounds of the general formula (I) according to Claim 1, in which

R^1 represents pyrimidinyl, pyridazinyl, pyridyl, pyrazinyl, tetrahydropyranyl, tetrahydrofuranyl, pyrrolyl, furyl, thienyl, imidazolyl, oxazolyl, thiazolyl, 1,2,3-triazolyl, pyrazolyl, oxadiazolyl, thiadiazolyl, isoxazolyl, isothiazolyl, pyranyl or morpholinyl, each of which is optionally substituted up to 3 times identically or differently by amino, formyl, mercaptyl, carboxyl, hydroxyl, straight-chain or branched acyl, alkoxy, alkylthio or alkoxycarbonyl each having up to 5 carbon atoms, nitro, cyano, azido, fluorine, chlorine, bromine, phenyl or straight-chain or branched alkyl having up to 5 carbon atoms, which for its part can be substituted by hydroxyl, amino, azido, carboxyl, straight-chain or branched acyl, alkoxy, alkoxycarbonyl or acylamino each having up to 4 carbon atoms or by a radical of the formula $-OR^4$,

in which

R^4 denotes straight-chain or branched acyl having up to 4 carbon atoms,

and/or by a radical of the formula



or

$-S(O)_c-NR^9R^{10}$,

in which

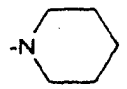
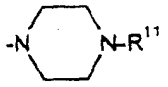
a, b and b' are identical or different and denote a number 0, 1, 2 or 3,

R^8 denotes hydrogen or straight-chain or branched alkyl having up to 3 carbon atoms,

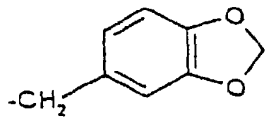
c denotes a number 1 or 2 and

R^9 and R^{10} are identical or different and denote hydrogen or straight-chain or branched alkyl having up to 9 carbon atoms, which can optionally be substituted by cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl or naphthyl or phenyl, which for their part can be substituted by fluorine or chlorine, or
denote phenyl or naphthyl, each of which is optionally substituted by fluorine or chlorine, or
denote cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl, or

R^9 and R^{10}, together with the nitrogen atom, form a morpholine ring or a radical of the formula


,  or  , in which

R^{11} denotes hydrogen, methyl or a radical of the formula


or denotes benzyl or phenyl,

where the ring systems are optionally substituted by fluorine or chlorine,

R^2 and R^3, including the double bond, form a pyridyl, pyrimidinyl, pyrazinyl or pyridazinyl ring, each of which is optionally substituted up to 3 times identically or differently by formyl, carboxyl, hydroxyl, mercaptyl,

straight-chain or branched acyl, alkylthio or alkoxycarbonyl each having up to 5 carbon atoms, nitro, cyano, azido, fluorine, chlorine, bromine or straight-chain or branched alkyl or alkoxy each having up to 5 carbon atoms, which for its part can be substituted by hydroxyl, amino, carboxyl, straight-chain or branched acyl, alkoxy or alkoxycarbonyl each having up to 4 carbon atoms,

and/or the abovementioned heterocyclic rings are optionally substituted by a group of the formula $-NR^{12}R^{13}$ or $-S(O)_{c'}NR^{9'}R^{10'}$, in which

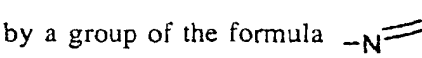
R^{12} and R^{13} are identical or different and denote hydrogen or straight-chain or branched alkyl having up to 4 carbon atoms, or

R^{12} denotes hydrogen and

R^{13} denotes formyl

c', $R^{9'}$ and $R^{10'}$ have the meaning of c, R^9 and R^{10} indicated above and are identical to or different from these

and/or the abovementioned heterocyclic rings are optionally substituted by phenyl, which for its part can be substituted by fluorine, chlorine, bromine or by straight-chain or branched alkyl or alkoxy each having up to 4 carbon atoms

and/or the abovementioned heterocyclic rings are optionally substituted by a group of the formula  , in which

R^{14} and R^{15} denote hydrogen or straight-chain or branched alkyl having up to 4 carbon atoms,

A represents thienyl, tetrahydropyranyl, tetrahydrofuranyl, phenyl, morpholinyl, pyrimidyl, pyrazinyl, pyridazinyl or pyridyl, each of which is optionally substituted up to 2 times identically or differently by hydroxyl, formyl, carboxyl, straight-chain or branched acyl, alkylthio, alkoxyacyl, alkoxy or alkoxycarbonyl each having up to 4 carbon atoms, fluorine, chlorine, bromine, nitro, cyano, trifluoromethyl or straight-chain or branched alkyl having up to 4 carbon atoms, which for its part can be substituted by hydroxyl, carboxyl, straight-chain or branched acyl, alkoxy or alkoxycarbonyl each having up to 4 carbon atoms,

and/or by a group of the formula $-(CO)_d-NR^{16}R^{17}$,

in which

d denotes a number 0 or 1,

R^{16} and R^{17} are identical or different and

denote hydrogen, phenyl, benzyl or straight-chain or branched alkyl or acyl each having up to 4 carbon atoms,

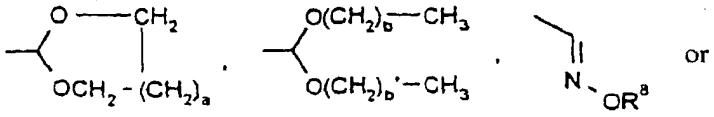
and their isomeric forms and salts.

3. Compounds of the general formula (I) according to Claim 1, in which

R^1 represents imidazolyl, furyl, pyridyl, pyrrolyl, pyrazinyl, pyrimidyl, isoxazolyl, oxazolyl or thiazolyl, each of which is optionally substituted up to 3 times identically or differently by formyl, fluorine, chlorine, amino, mercaptyl, cyano, straight-chain or branched acyl, alkylthio, alkoxy or alkoxycarbonyl each having up to 4 carbon atoms or straight-chain or branched alkyl having up to 4 carbon atoms, which for its part can be substituted by hydroxyl, carboxyl, amino, azido, straight-chain or branched acyl, alkoxy, alkoxycarbonyl or acylamino each having up to

3 carbon atoms,

and/or by a radical of the formula



$-S(O)_c-NR^9R^{10}$,

in which

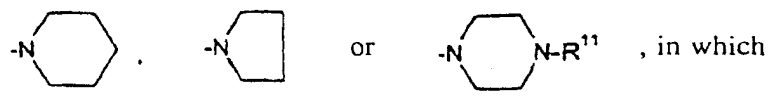
a, b and b' are identical or different and denote a number 0, 1 or 2,

R^8 denotes hydrogen or methyl,

c denotes a number 1 or 2 and

R^9 and R^{10} are identical or different and denote hydrogen or straight-chain or branched alkyl having up to 9 carbon atoms, which can optionally be substituted by phenyl or naphthyl, or
denote phenyl or naphthyl, each of which is optionally substituted by fluorine or chlorine, or
denote cyclopropyl or cycloheptyl, or

R^9 and R^{10}, together with the nitrogen atom, form a morpholine ring or a radical of the formula



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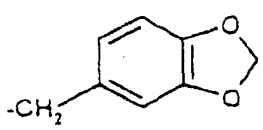
R^{11} denotes hydrogen, methyl or a radical of the formula



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ring systems are optionally substituted by chlorine,

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and/or the heterocyclic rings are optionally substituted by amino, N,N-dimethylamino or by a radical of the formula -NH-CHO or $-N=CH-N(CH_3)_2$ and/or by phenyl, which for its part can be substituted by a radical of the formula $-O(CH_2)_2-CH_3$,

A represents tetrahydropyranyl, phenyl, pyrimidyl, thienyl or pyridyl, each of which is optionally substituted up to 2 times identically or differently by formyl, carboxyl, straight-chain or branched acyl, alkylthio, alkyloxyacyl, alkoxy or alkoxycarbonyl each having up to 3 carbon atoms, fluorine, chlorine, bromine, nitro, cyano, trifluoromethyl or straight-chain or branched alkyl having up to 3 carbon atoms, which for its part can be substituted by hydroxyl, carboxyl, straight-chain or branched acyl, alkoxy or alkoxycarbonyl each having up to 3 carbon atoms,

and their isomeric forms and salts.

4. Process for the preparation of compounds of the general formula (I) according to Claim 1, characterized in that, depending on the various meanings of the heterocycles defined under R^2 and R^3, either

[A] compounds of the general formula (II)

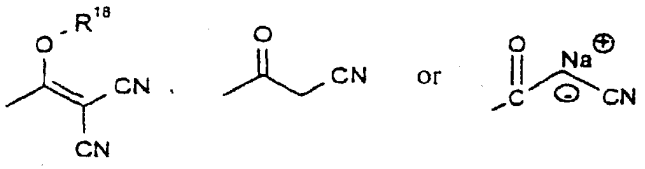
$$R^1\text{-}D \qquad (II)$$

in which

R^1 has the meaning indicated above,

and

D represents radicals of the formula



in which

R^{18} represents C_1-C_4-alkyl,

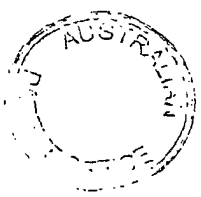
are converted by reaction with compounds of the general formula (III)

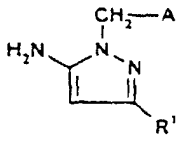
$$A\text{-}CH_2\text{-}NH\text{-}NH_2 \qquad (III)$$

in which

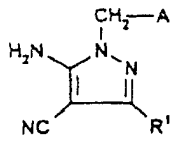
A has the meaning indicated above

in inert solvents, if appropriate in the presence of a base, into the compounds of the general formula (IV) or (IVa)





(IV) and



(IVa)

in which

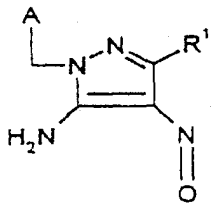
A and R^1 have the meaning indicated above,

and, in the case of the compounds of the general formula (IVa), then cyclized with carboxylic acids, nitriles, formamides or guanidinium salts,

and, in the case of the compounds of the general formula (IV), cyclized with 1,3-dicarbonyl derivatives, their salts, tautomers, enol ethers or enamines, in the presence of acids and, if appropriate, under microwaves,

or

[B] in the case where R^2 and R^3 together form a pyrazine ring, compounds of the general formula (IV) are first converted by nitrosation into the compounds of the general formula (V)



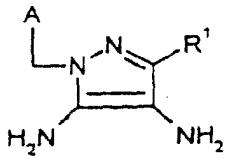
(V),

in which

A and R^1 have the meaning indicated above,

in a second step, by means of a reduction, the compounds of the general

formula (VI)



(VI),

in which

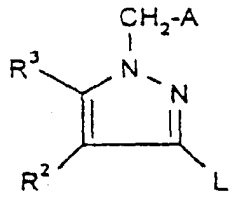
A and R^1 have the meaning indicated above,

are prepared

and finally cyclized with 1,2-dicarbonyl compounds, preferably aqueous glyoxal solution,

or

[C] compounds of the general formula (VII)



(VII)

in which

A^1, R^2 and R^3 have the meaning indicated above,

and

L represents a radical of the formula $-SnR^{19}R^{20}R^{21}$, ZnR^{22}, iodine, bromine or triflate,

in which

R^{19}, R^{20} and R^{21} are identical or different and denote straight-chain or branched alkyl having up to 4 carbon atoms,

and

R^{22} denotes halogen,

are reacted with compounds of the general formula (VIII)

$$R^1\text{-}T \qquad \text{(VIII)}$$

in which

R^1 has the meaning indicated above

and

if L = $SnR^{19}R^{20}R^{21}$ or ZnR^{22}

T represents triflate or halogen, preferably bromine,

and

if L = iodine, bromine or triflate,

T represents a radical of the formula $SnR^{19'}R^{20'}R^{21'}$, $ZnR^{22'}$ or $BR^{23'}R^{24'}$,

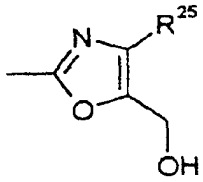
in which

$R^{19'}$, $R^{20'}$, $R^{21'}$ and $R^{22'}$ have the meaning of R^{19}, R^{20}, R^{21} and R^{22} indicated above and are identical to or different from

these,

$R^{23'}$ and $R^{24'}$ are identical or different and denote hydroxyl, aryloxy having 6 to 10 carbon atoms or straight-chain or branched alkyl or alkoxy each having up to 5 carbon atoms, or together form a 5- or 6-membered carbocyclic ring,

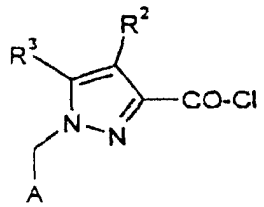
in a palladium-catalysed reaction in inert solvents, if appropriate in the presence of a base,

[D] if R^1 = 

in which

R^{25} denotes (C_1-C_6)-alkyl which is optionally substituted by halogen,

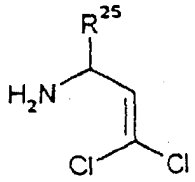
compounds of the general formula (IX)

 (IX),

in which

A, R^2 and R^3 have the meaning indicated above,

are converted either directly by reaction with the compound of the formula (X)



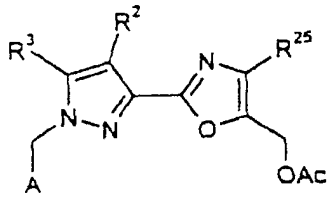
(X)

in which

R^{25} has the meaning indicated above,

in the system $NaOCO-CH_3$/N-methylpyrrolidine

into the compounds of the general formula (Ia)



(Ia),

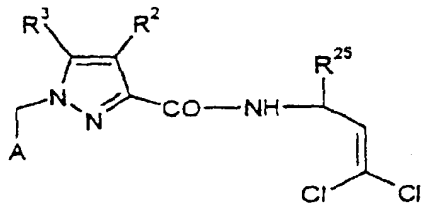
in which

R^2, R^3 and A and R^{25} have the meaning indicated above,

and then, by action of potassium hydroxide in methanol, the acetyl group is removed,

or

first, by reaction of the compounds of the general formula (IX) with the compound of the formula (X), the compounds of the general formula (XI)



(XI),

in which

R^2, R^3, A and R^{25} have the meaning indicated above,

are prepared,

and in a further step, by action of potassium hydroxide, the hydroxymethyl compounds are prepared,

and, if appropriate, converted into the corresponding alkoxy compounds by alkylation according to customary methods,

and in the case of the groups $-S(O)_cNR^9R^{10}$ and $-S(O)_cNR^{9'}R^{10'}$, starting from the unsubstituted compounds of the general formula (I), first reacted with thionyl chloride and in a second step with the appropriate amines

and, if appropriate, the substituents mentioned under R^1, R^2, R^3 and/or A are varied or introduced according to customary methods, preferably by chlorination, catalytic hydrogenation, reduction, oxidation, removal of protective groups and/or nucleophilic substitution.

5. Medicaments comprising at least one compound of the general formula (I) according to Claim 1.

6. Process for the production of medicaments, characterized in that at least one

compound of the formula (I) according to Claim 1 is converted into a suitable administration form, if appropriate using customary auxiliaries and additives.

7. Medicaments comprising at least one compound of the general formula (I) according to Claim 1 in combination with organic nitrates or NO donors.

8. Medicaments comprising at least one compound of the general formula (I) according to Claim 1 in combination with compounds which inhibit the degradation of cyclic guanosine monophosphate (cGMP).

9. Use of compounds of the general formula (I) according to Claim 1 in the production of medicaments for the treatment of cardiovascular disorders.

10. Use of compounds of the general formula (I) according to Claim 1 in the production of medicaments for the treatment of thromboembolic disorders and ischaemias.